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(FILE 'HOME' ENTERED AT 18:05:28 ON 19 AUG 2004)

FILE 'MEDLINE, CAPLUS, BIOSIS, SCISEARCH' ENTERED AT 18:05:42 ON 19 AUG 2004

L1 3086 S FABRY(W)DISEASE
L2 142 S (REDUC? OR DECREAS? OR DIMINISH? OR INHIBIT?)(7A)(GLOBOTRIAOS
L3 91763 S GALACTOSIDASE
L4 80 S L2 AND L3
L5 20 S L2(8A)L3
L6 9 DUP REM L5 (11 DUPLICATES REMOVED)

=> d au ti so pi ab 1-9 l6

L6 ANSWER 1 OF 9 MEDLINE on STN DUPLICATE 1
AU Przybylska Malgorzata; Wu I-Huan; Zhao Hongmei; Ziegler Robin J; Tousignant Jennifer D; Desnick Robert J; Scheule Ronald K; Cheng Seng H; Yew Nelson S
TI Partial correction of the alpha-galactosidase A deficiency and reduction of glycolipid storage in Fabry mice using synthetic vectors.
SO journal of gene medicine, (2004 Jan) 6 (1) 85-92.
Journal code: 9815764. ISSN: 1099-498X.
AB BACKGROUND: Fabry disease is a recessive, X-linked disorder caused by a deficiency of the lysosomal enzyme alpha-galactosidase A, leading to an accumulation of the glycosphingolipid globotriaosylceramide (GL-3) in most tissues of the body. The goal of this study was to determine if systemic delivery of a nonviral vector could correct the enzyme deficiency and reduce the levels of GL-3 in different tissues of a transgenic knockout mouse model of the disease. METHODS: Cationic lipid was complexed with a CpG-depleted plasmid DNA vector and then injected intravenously into Fabry mice. The levels of alpha-galactosidase A and GL-3 in different tissues were assayed at various time points after injection. RESULTS: Expression of alpha-galactosidase A was detected in the different tissues of Fabry mice for up to 3 months after complex administration, but resulted in minimal reductions in GL-3 levels. However, the use of the anti-inflammatory drug dexamethasone and multiple dosing increased alpha-**galactosidase** A expression and resulted in significant **reductions** of **GL-3** in all the organs with the exception of the kidney. In addition, injecting complex into young Fabry mice partially prevented the normal accumulation of GL-3 in the heart, lung, and liver. CONCLUSIONS: Systemic delivery of a cationic lipid-pDNA complex partially corrected the enzyme deficiency and reduced glycolipid storage in a mouse model of Fabry disease. The results are one of the few demonstrations of long-term efficacy in a genetic disease model using nonviral vectors. However, substantial improvements in expression, especially in critical organs such as the kidney, are required before these vectors can become a viable approach to treat Fabry disease and other lysosomal storage disorders.

L6 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2004 ACS on STN
AU Hughes, Alisa K.; Ergonul, Zuhal; Stricklett, Peter K.; Kohan, Donald E.
TI Molecular basis for high renal cell sensitivity to the cytotoxic effects of shigatoxin-1: upregulation of globotriaosylceramide expression. [Erratum to document cited in CA137:334170]
SO Journal of the American Society of Nephrology (2003), 14(5), No pp. given
CODEN: JASNEU; ISSN: 1046-6673
AB The name of the second author, Z. Ergonul, was misspelled.

L6 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2004 ACS on STN
AU Hughes, Alisa K.; Ergonal, Zuhal; Stricklett, Peter K.; Kohan, Donald E.
TI Molecular basis for high renal cell sensitivity to the cytotoxic effects of shigatoxin-1: upregulation of globotriaosylceramide expression

SO Journal of the American Society of Nephrology (2002), 13(9), 2239-2245
CODEN: JASNEU; ISSN: 1046-6673

AB Cellular injury in post-diarrheal hemolytic-uremic syndrome (D+HUS) is related to shigatoxin (Stx) binding to globotriaosylceramide (Gb3). High renal Gb3 expression may determine renal susceptibility in D+HUS; however, the mol. mechanism(s) responsible for such relatively abundant Gb3 levels are unknown. Consequently, kidney cells expressing high Gb3 (cultured human proximal tubule cells [HPT]) were compared with non-kidney cells with low Gb3 content (cultured human brain microvascular endothelial cells [HBEC]). HPT were much more sensitive to the cytotoxic and protein synthesis inhibitory effects of Stx-1; this correlated with Gb3 content and 125I-Stx-1 binding. HPT had greater Gb3 synthase (GalT6) and lower α-galactosidase activities than HBEC, whereas lactosylceramide synthase (GalT2) activity was higher in HBEC. Ceramide glucosyltransferase (CGT) activity was similar between the two cell types. The higher HPT GalT6 activity was associated with increased GalT6 mRNA steady-state levels, but no difference in GalT6 mRNA half-life. The lower HPT α-galactosidase activity was associated with reduced α-galactosidase mRNA steady-state levels but no difference in α-galactosidase mRNA half-life. Higher HBEC GalT2 activity was associated with increased steady-state GalT2 mRNA levels. These studies suggest that high renal Gb3 expression is due to enhanced GalT6 gene transcription and reduced α-galactosidase gene transcription and occur despite relatively low GalT2 activity.

L6 ANSWER 4 OF 9 MEDLINE on STN DUPLICATE 2

AU Li Chester; Ziegler Robin J; Cherry Maribeth; Lukason Michael; Desnick Robert J; Yew Nelson S; Cheng Seng H

TI Adenovirus-transduced lung as a portal for delivering alpha-galactosidase A into systemic circulation for Fabry disease.

SO Molecular therapy : journal of the American Society of Gene Therapy, (2002 Jun) 5 (6) 745-54.
Journal code: 100890581. ISSN: 1525-0016.

AB Gene therapy efforts have focused primarily on the use of either the liver or skeletal muscle as depot organs for the production of a variety of therapeutic proteins that act systemically. Here we examined the lung to determine whether it could function as yet another portal for the secretion of proteins into the circulation. Fabry disease is caused by a deficiency of the lysosomal hydrolase alpha-galactosidase A, resulting in the abnormal deposition of the glycosphingolipid globotriaosylceramide (GL-3) in vascular lysosomes. Pulmonary instillation of a recombinant adenoviral vector (Ad2/CMVHI-alpha(gal)) encoding human alpha-galactosidase A into Fabry mice resulted in high-level transduction and expression of the enzyme in the lung. Importantly, enzymatic activity was also detected in the plasma, liver, spleen, heart, and kidneys of the Fabry mice. The detection of enzymatic activity outside of the lung, along with the finding that viral DNA was limited to the lung, indicates that the enzyme crossed the air/blood barrier, entered the systemic circulation, and was internalized by the distal visceral organs. The levels of alpha-**galactosidase** A attained in these tissues were sufficient to **reduce GL-3** to basal levels in the lung, liver, and spleen and to approximately 50% of untreated levels in the heart. Together, these results suggest that the lung may be a viable alternate depot organ for the production and systemic secretion of alpha-galactosidase A for Fabry disease.

L6 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2004 ACS on STN

AU Branton, Mary H.; Schiffmann, Raphael; Sabnis, Sharda G.; Murray, Gary J.; Quirk, Jane M.; Altarescu, Gheona; Goldfarb, Lev; Brady, Roscoe O.; Balow, James E.; Austin, Howard A., III; Kopp, Jeffrey B.

TI Natural history of Fabry renal disease: Influence of α-galactosidase A activity and genetic mutations on clinical course

SO Medicine (Baltimore, MD, United States) (2002), 81(2), 122-138

CODEN: MEDIAV; ISSN: 0025-7974

AB We discuss the medical records of 105 male patients with Fabry disease. We describe the clin. course and histol. of their renal disease and correlate them with residual α-galactosidase A (α gal A) activity and with mutations in the α-gal A gene. Hemizygous male patients with Fabry disease may develop proteinuria and chronic renal insufficiency in adolescence or early adulthood. By age 35 yr, 50% of patients had non-nephrotic range proteinuria and almost 20% had early renal insufficiency. 50% Of surviving patients had renal insufficiency by age 42 yr, and 50% had progressed to end-stage renal disease by age 47 yr. 23% Of all patients eventually developed end-stage renal disease. By age 55 yr, 500% of the patients had died, and all had died by age 60 yr. Nephrotic proteinuria was present in 18% of patients and hypertension was present in 30% of patients. Either manifestation may appear before or after the onset of chronic renal insufficiency. After the onset of chronic renal insufficiency, the mean rate of change in glomerular filtration rate was -12.2 mL/min per yr with patients reaching end-stage renal disease after 4.1 yr. The presence of detectable residual α gal A activity in peripheral leukocytes was associated with a later onset of chronic renal insufficiency, lower renal globotriaosylceramide content, and lower scores for renal histol. damage. Conservative missense mutations were associated with longer renal survival compared with nonconservative missense or other mutations.

L6 ANSWER 6 OF 9 MEDLINE on STN DUPLICATE 3

AU Eng C M; Guffon N; Wilcox W R; Germain D P; Lee P; Waldek S; Caplan L; Linthorst G E; Desnick R J

TI Safety and efficacy of recombinant human alpha-galactosidase A--replacement therapy in Fabry's disease.

SO New England journal of medicine, (2001 Jul 5) 345 (1) 9-16. Journal code: 0255562. ISSN: 0028-4793.

AB BACKGROUND: Fabry's disease, lysosomal alpha-galactosidase A deficiency, results from the progressive accumulation of globotriaosylceramide and related glycosphingolipids. Affected patients have microvascular disease of the kidneys, heart, and brain. METHODS: We evaluated the safety and effectiveness of recombinant alpha-galactosidase A in a multicenter, randomized, placebo-controlled, double-blind study of 58 patients who were treated every 2 weeks for 20 weeks. Thereafter, all patients received recombinant alpha-galactosidase A in an open-label extension study. The primary efficacy end point was the percentage of patients in whom renal microvascular endothelial deposits of globotriaosylceramide were cleared (reduced to normal or near-normal levels). We also evaluated the histologic clearance of microvascular endothelial deposits of globotriaosylceramide in the endomyocardium and skin, as well as changes in the level of pain and the quality of life. RESULTS: In the double-blind study, 20 of the 29 patients in the recombinant alpha-galactosidase A group (69 percent) had no microvascular endothelial deposits of globotriaosylceramide after 20 weeks, as compared with none of the 29 patients in the placebo group (P<0.001). Patients in the recombinant alpha-**galactosidase** A group also had **decreased** microvascular endothelial deposits of **globotriaosylceramide** in the skin (P<0.001) and heart (P<0.001). Plasma levels of globotriaosylceramide were directly correlated with clearance of the microvascular deposits. After six months of open-label therapy, all patients in the former placebo group and 98 percent of patients in the former recombinant alpha-galactosidase A group who had biopsies had clearance of microvascular endothelial deposits of globotriaosylceramide. The incidence of most treatment-related adverse events was similar in the two groups, with the exception of mild-to-moderate infusion reactions (i.e., rigors and fever), which were more common in the recombinant alpha-galactosidase A group. IgG seroconversion occurred in 88 percent of patients who received recombinant alpha-galactosidase A. CONCLUSIONS: Recombinant alpha-galactosidase A replacement therapy cleared microvascular endothelial deposits of

globotriaosylceramide from the kidneys, heart, and skin in patients with Fabry's disease, reversing the pathogenesis of the chief clinical manifestations of this disease.

L6 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 4
AU Abe, Akira; Gregory, Susan; Lee, Lihsueh; Killen, Paul D.; Brady, Roscoe O.; Kulkarni, Ashok; Shayman, James A.
TI Reduction of globotriaosylceramide in Fabry disease mice by substrate deprivation
SO Journal of Clinical Investigation (2000), 105(11), 1563-1571
CODEN: JCINAO; ISSN: 0021-9738
AB We used a potent inhibitor of glucosylceramide synthase to test whether substrate deprivation could lower globotriaosylceramide levels in α-galactosidase A (α-gal A) knockout mice, a model of Fabry disease. C57BL/6 mice treated twice daily for 3 days with D-threo-1-ethylendioxyphenyl-2-palmitoylamino-3-pyrrolidino-propanol (D-t-EtDO-P4) showed a concentration-dependent decrement in glucosylceramide levels in kidney, liver, and spleen. A single i.p. injection of D-t-EtDO-P4 resulted in a 55% reduction in renal glucosylceramide, consistent with rapid renal glucosylceramide metabolism A concentration-dependent decrement in renal and hepatic globotriaosylceramide levels was observed in α-Gal A- males treated for 4 wk with D-t-EtDO-P4. When 8-wk-old α-Gal A- males were treated for 8 wk with 10 mg/kg twice daily, renal globotriaosylceramide fell to below starting levels, consistent with an α-galactosidase A-independent salvage pathway for globotriaosylceramide degradation Complications observed with another glucosylceramide synthase inhibitor, N-butyldeoxynojirimycin, including weight loss and acellularity of lymphatic organs, were not observed with D-t-EtDO-P4. These data suggest that Fabry disease may be amenable to substrate deprivation therapy.

L6 ANSWER 8 OF 9 MEDLINE on STN DUPLICATE 5
AU Schiffmann R; Murray G J; Treco D; Daniel P; Sellos-Moura M; Myers M; Quirk J M; Zirzow G C; Borowski M; Loveday K; Anderson T; Gillespie F; Oliver K L; Jeffries N O; Doo E; Liang T J; Kreps C; Gunter K; Frei K; Crutchfield K; Selden R F; Brady R O
TI Infusion of alpha-**galactosidase** A **reduces** tissue **globotriaosylceramide** storage in patients with Fabry disease.
SO Proceedings of the National Academy of Sciences of the United States of America, (2000 Jan 4) 97 (1) 365-70.
Journal code: 7505876. ISSN: 0027-8424.
AB Fabry disease is a lysosomal storage disorder caused by a deficiency of the lysosomal enzyme alpha-galactosidase A (alpha-gal A). This enzymatic defect results in the accumulation of the glycosphingolipid globotriaosylceramide (Gb(3); also referred to as ceramidetrihexoside) throughout the body. To investigate the effects of purified alpha-gal A, 10 patients with Fabry disease received a single i.v. infusion of one of five escalating dose levels of the enzyme. The objectives of this study were: (i) to evaluate the safety of administered alpha-gal A, (ii) to assess the pharmacokinetics of i.v.-administered alpha-gal A in plasma and liver, and (iii) to determine the effect of this replacement enzyme on hepatic, urine sediment and plasma concentrations of Gb(3). alpha-Gal A infusions were well tolerated in all patients. Immunohistochemical staining of liver tissue approximately 2 days after enzyme infusion identified alpha-gal A in several cell types, including sinusoidal endothelial cells, Kupffer cells, and hepatocytes, suggesting diffuse uptake via the mannose 6-phosphate receptor. The tissue half-life in the liver was greater than 24 hr. After the single dose of alpha-gal A, nine of the 10 patients had significantly reduced Gb(3) levels both in the liver and shed renal tubular epithelial cells in the urine sediment. These data demonstrate that single infusions of alpha-gal A prepared from transfected human fibroblasts are both safe and biochemically active in patients with Fabry disease. The degree of substrate reduction seen in

the study is potentially clinically significant in view of the fact that Gb(3) burden in Fabry patients increases gradually over decades. Taken together, these results suggest that enzyme replacement is likely to be an effective therapy for patients with this metabolic disorder.

L6 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2004 ACS on STN

AU Ziegler, Robin J.; Yew, Nelson S.; Li, Chester; Cherry, Maribeth; Berthelette, Patricia; Romanczuk, Helen; Ioannou, Yiannis A.; Zeidner, Kenneth M.; Desnick, Robert J.; Cheng, Seng H.

TI Correction of enzymatic and lysosomal storage defects in Fabry mice by adenovirus-mediated gene transfer

SO Human Gene Therapy (1999), 10(10), 1667-1682
CODEN: HGTHE3; ISSN: 1043-0342

AB Fabry disease is a recessive, X-linked disorder caused by a deficiency of the lysosomal hydrolase α-galactosidase A. Deficiency of this enzyme results in progressive deposition of the glycosphingolipid globotriaosylceramide (GL-3) in the vascular lysosomes, with resultant distension of the organelle. The demonstration of a secretory pathway for lysosomal enzymes and their subsequent recapture by distant cells through the mannose 6-phosphate receptor pathway has provided a rationale for somatic gene therapy of lysosomal storage disorders. Toward this end, recombinant adenoviral vectors encoding human α-galactosidase A (Ad2/CEHα-Gal, Ad2/CMVHIα-Gal) were constructed and injected i.v. into Fabry knockout mice. Administration of Ad2/CEHα-Gal to the Fabry mice resulted in an elevation of α-galactosidase A activity in all tissues, including the liver, lung, kidney, heart, spleen, and muscle, to levels above those observed in normal animals. However, enzymic expression declined rapidly such that by 12 wk, only 10% of the activity observed on day 3 remained. α-Galactosidase A detected in the plasma of injected animals was in a form that was internalized by Fabry fibroblasts grown in culture. Such internalization occurred via the mannose 6-phosphate receptors. Importantly, concomitant with the increase in enzyme activity was a significant reduction in GL-3 content in all tissues to near normal levels for ≤6 mo posttreatment. However, as expression of α-galactosidase A declined, low levels of GL-3 reaccumulated in some of the tissues at 6 mo. For protracted treatment, the authors showed that readministration of recombinant adenovirus vectors could be facilitated by transient immunosuppression using a monoclonal antibody against CD40 ligand (MR1). Together, these data demonstrate that the defects in α-galactosidase A activity and lysosomal storage of GL-3 in Fabry mice can be corrected by adenovirus-mediated gene transfer. This suggests that gene replacement therapy represents a viable approach for the treatment of Fabry disease and potentially other lysosomal storage disorders.

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☐ 1. 20040110709. 01 Aug 03. 10 Jun 04. Genetic modification of the lung as a portal for gene delivery. Li, Chester, et al. 514/44; A61K048/00.

☐ 2. 20010036454. 15 Feb 01. 01 Nov 01. Genetic modification of the lung as a portal for gene delivery. Li, Chester, et al. 424/93.21; 424/43 514/44 A61K048/00 A61L009/04 A61K009/00.

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☐ 1. 20040110709. 01 Aug 03. 10 Jun 04. Genetic modification of the lung as a portal for gene delivery. Li, Chester, et al. 514/44; A61K048/00.

☐ 2. 20030119874. 26 Nov 02. 26 Jun 03. Method for enhancing mutant enzyme activity in gaucher disease. Fan, Jian-Qiang, et al. 514/317; 514/328 A61K031/445.

☐ 3. 20020095135. 19 Jun 01. 18 Jul 02. Combination enzyme replacement, gene therapy and small molecule therapy for lysosomal storage diseases. Meeker, David, et al. 604/522; A61M031/00.

☐ 4. 20020035072. 07 Sep 01. 21 Mar 02. Method for enhancing mutant enzyme activities in lysosomal storage disorders. Fan, Jian-Qiang, et al. 514/25; 514/277 514/28 514/281 514/315 A61K031/70 A61K031/435 A61K031/445.

☐ 5. 20010036454. 15 Feb 01. 01 Nov 01. Genetic modification of the lung as a portal for gene delivery. Li, Chester, et al. 424/93.21; 424/43 514/44 A61K048/00 A61L009/04 A61K009/00.

☐ 6. 20010031741. 06 Feb 01. 18 Oct 01. Methods for treatment of lysosomal storage diseases. Ziegler, Robin, et al. 514/44; 424/94.61 514/102 A61K048/00 A61K038/47 A61K031/663.

☐ 7. 6599919. 07 Sep 01; 29 Jul 03. Method for enhancing mutant enzyme activities in lysosomal storage disorders. Fan; Jian-Qiang, et al. 514/315; 435/208. A61K031/445.

☐ 8. 6583158. 26 Jun 00; 24 Jun 03. Method for enhancing mutant enzyme activities in lysosomal storage disorders. Fan; Jian-Qiang, et al. 514/315; 424/94.61 435/206 435/208 514/25 514/277 514/28 514/281. A61K031/445 A61K031/70 A61K031/435.

☐ 9. 6413768. 02 Dec 98; 02 Jul 02. Expression plasmids. Galen; James E.. 435/320.1; 530/300 530/350 530/403 536/24.1. C12N015/63.

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